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Corresponding author(s): Jordane Dimidschstein

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# Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

## Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

| n/a | Confirmed |
|---|---|
| ☐ | ☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement |
| ☐ | ☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ The statistical test(s) used AND whether they are one- or two-sided<br>*Only common tests should be described solely by name; describe more complex techniques in the Methods section.* |
| ☐ | ☒ A description of all covariates tested |
| ☐ | ☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| ☐ | ☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| ☐ | ☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted<br>*Give P values as exact values whenever suitable.* |
| ☒ | ☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| ☒ | ☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| ☒ | ☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated |

*Our web collection on statistics for biologists contains articles on many of the points above.*

## Software and code

Policy information about availability of computer code

| | |
|---|---|
| Data collection | No software was used to collect the data |
| Data analysis | - ImageJ (v1.8.0) was used to manipulate images and perform co-localization analysis.<br>- 10X Cell-Ranger (v1.1.0) was used to process the scATACseq data.<br>- snapATAC (v1) was used as the Analysis Pipeline for Single Cell ATAC-seq<br>- macs2 (v2.2.7.1) was used to call peaks from the scATACseq data.<br>- bedtools (v 2.28.0) was used to identify enhancer sequances<br>- Integrated genome browser v2.3 was used to visualize the bed files generated for enhancer identification<br>- EMBOSS Needle (https://www.ebi.ac.uk/Tools/psa/emboss_needle/) was used to align and compare enhancer sequences between mice and humans.<br>- CiiiDER pipeline (http://ciiider.com) was used to analyze transcription binding site enrichment in the indicated enhancer sequences.<br>- Clampfit software (v10.2) was used to analysis electrophysiological recordings. |

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

## Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. The scATAC datasets presented in the study (figure 1 and supplementary figure 1) are available on GEO with the accession number GSE152449. All AAV plasmids and their corresponding sequences are available on Addgene (pAAV-S5E2-dTom-nlsdTom Addgene#135630; pAAV-S5E2-GFP-fGFP Addgene#135631; pAAV-S5E2-GCaMP6f Addgene#135632; pAAV-S5E2-C1V1-eYFP Addgene#135633; pAAV-S5E2-ChR2-mCherry Addgene#135634; pAAV-S5E2-Gq-P2A-dTomato-short Addgene#135635; pAAV-S5E1-dTom-nlsdTom Addgene#135637; pAAV-S5E3-dTom-nlsdTom Addgene#135638; pAAV-S5E4-dTom-nlsdTom Addgene#135639; pAAV-S5E5-dTom-nlsdTom Addgene#135640; pAAV-S5E6-dTom-nlsdTom Addgene#135641; pAAV-S5E7-dTom-nls-dTom Addgene#135642; pAAV-S5E8-dTom-nlsdTom Addgene#135643; 018_pAAV-S5E9-dTom-nls-dTom Addgene#135644; pAAV-S5E10-dTom-nlsdTom Addgene#135645; pAAV-E11-ChR2GFP2x Addgene#153434; pAAV-E14-ChR2GFP2x Addgene#153435; pAAV-E22-ChR2GFP2x Addgene#153436; pAAV-E29-ChR2GFP2x Addgene#153437).

# Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

# Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

| | |
|---|---|
| Sample size | No statistical method was used to determine the sample size. We selected the highest number of samples we could perform under reasonable financial and logistical constraints to provide precise and accurate estimates of the data's central tendency and variance and allow for the computational of confidence intervals around estimates, with at least 2 biological replicates per conditions. |
| Data exclusions | The staining of PV IHC within human brain tissues was highly variable. As such, estimates of viral specificity were made within regions of cortex and subiculum where staining density was reflective of the known distribution and density of these cells. Sections where the PV-IHC was not reflective of the know distribution of these cells were excluded from the study. |
| Replication | At least two biological replicates per data point were included for all quantification presented in this study. In all cases where the number of biological replicates was not above 2, the replicates were highly consistent. For ethical and economic reasons, the data generated for systemic viral injection in a marmoset and for local injection in macaques come from a unique animal and was not repeated. |
| Randomization | No condition tested in this study required control versus test groups and thus no randomization was relevant |
| Blinding | No condition tested in this study required control versus test groups, as such blinding was not relevant to the study. |

# Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

## Materials & experimental systems

| n/a | Involved in the study |
|---|---|
| ☐ | ☒ Antibodies |
| ☒ | ☐ Eukaryotic cell lines |
| ☒ | ☐ Palaeontology and archaeology |
| ☐ | ☒ Animals and other organisms |
| ☐ | ☒ Human research participants |
| ☐ | ☒ Clinical data |
| ☒ | ☐ Dual use research of concern |

## Methods

| n/a | Involved in the study |
|---|---|
| ☒ | ☐ ChIP-seq |
| ☒ | ☐ Flow cytometry |
| ☒ | ☐ MRI-based neuroimaging |

## Antibodies

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| Antibodies used | chicken anti-GFP at 1:1,000 (Abcam USA, ab13970); rabbit anti-DsRed at 1:1,000 (Clontech USA 632496); goat anti-PV at 1:1,000 (Swant USA, PVG-213); guinea-pig anti-PV at 1:2,000 (Swant USA, GP-72); rabbit anti-SST at 1:2,000 (Peninsula USA, T-4103.0050); mouse anti-Synaptotagmin-2 at 1:250 (ZFIN USA, #ZDB-ATB-081002-25) |
| Validation | All antibodies used in this study are commercially available and have been validated by the manufacturer. In addition to the validation statement that can be found by consulting the manufacturer's website using the references provided below, the specificity of each primary antibody used in these study was validated for the species for which it was used based on examining the signal intensity, the density of staining and the consistency with morphological features of the cellular populations and are presented in the relevant panels across the figures and supplementary figures of the manuscript.<br><br>chicken anti-GFP at 1:1,000 (Abcam USA, ab13970);<br>rabbit anti-DsRed at 1:1,000 (Clontech USA 632496);<br>goat anti-PV at 1:1,000 (Swant USA, PVG-213);<br>guinea-pig anti-PV at 1:2,000 (Swant USA, GP-72);<br>rabbit anti-SST at 1:2,000 (Peninsula USA, T-4103.0050);<br>mouse anti-Synaptotagmin-2 at 1:250 (ZFIN USA, #ZDB-ATB-081002-25) |

## Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

| | |
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| Laboratory animals | Mice. Female C57BL/6J mice (Mus musculus; 10 weeks old) were obtained from Jackson Labs (Bar Harbor, ME - stock# 000664). Male hemizygous Dlx6a-cre mice (Mus musculus; 10 weeks old - Jax stock #008199) and female homozygous INTACT mice (Mus musculus; 10 weeks old - flox-Sun1-eGFP, Jax stock #021039). Mice were maintained at macroenvironmental temperature and humidity ranges of 64 to 79 °F (17.8 to 26.1 °C) and 30% to 70%, respectively. These parameters were monitored closely and controlled within rodent colony rooms. Rat. Sprague Dawley rats (Rattus norvegicus, 12 weeks old 150-250g) were obtained from Charles River labs, Kingston, NY. Marmosets. One female common marmoset (Callithrix jacchus, 6.0 years old) was obtained from the colony at Massachusetts Institute of Technology. Macaques. Adult (2 years old) male macaques (Macaca mulatta) were obtained from the California National Primate Research Center at the University of California, Davis. All the animals were maintained in a 12 light/12 dark cycle with a maximum of five animals per cage for mice and one animal per cage for rats at . Marmosets and macaques were socially housed. All animal maintenance and experimental procedures were performed according to the guidelines established by the Institutional Animal Care and Use Committee at the Broad Institute of MIT and Harvard (mice), McGovern research institute at MIT (rats and marmosets) and Salk Institute for Biological studies (macaques). |
| Wild animals | This study did not involve wild animals. |
| Field-collected samples | This study did not involve samples collected from the field. |
| Ethics oversight | All animal maintenance and experimental procedures were performed according to the guidelines established by the Institutional Animal Care and Use Committee at the Broad Institute of MIT and Harvard (mice), McGovern research institute at MIT (rats and marmosets) and Salk Institute for Biological studies (macaques). |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

## Human research participants

Policy information about studies involving human research participants

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|---|---|
| Population characteristics | Four participants (2 male / 2 female; age range 22-57 years) underwent a surgical procedure in which brain tissue (temporal lobe and hippocampus) was resected for the treatment of drug resistant epilepsy. In all cases, each participant had previously undergone an initial surgery for placement of subdural and/or depth electrodes for intracranial monitoring in order to identify the location of seizure onset. |
| Recruitment | Patients were selected based on their need for treatment of drug resistant epilepsy by resection surgery. Any self-selection bias that might have occurred is unlikely to have consequence on the results presented in this study: the brain tissue used for the study was collected at the margins of the epileptic focus and exposed to adeno-associated virus ex-vivo and no parameters directly relevant to seizures needed to be recorded in the context of this study. Notably, the results obtained were consistent across males and females participants and across the age range representative of adult mature cortical tissue. |
| Ethics oversight | The NINDS Institutional Review Board (IRB) approved the research protocol (ClinicalTrials.gov Identifier NCT01273129), and we obtained informed consent from the participants for experimental use of the ressected tissue. |

Note that full information on the approval of the study protocol must also be provided in the manuscript.

# Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

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|---|---|
| Clinical trial registration | NCT01273129 |
| Study protocol | https://clinicaltrials.gov/ct2/show/NCT01273129 |
| Data collection | Study Type : Observational<br>Estimated Enrollment : 300 participants<br>LLocation: Observational Model: Cohort<br>Time Perspective: Prospective<br>Official Title: Surgery as a Treatment for Medically Intractable Epilepsy<br>Actual Study Start Date : December 7, 2010<br>United States, Maryland<br>National Institutes of Health Clinical Center, 9000 Rockville Pike Recruiting<br>Bethesda, Maryland, United States, 20892<br>Contact: For more information at the NIH Clinical Center contact Office of Patient Recruitment (OPR) 800-411-1222 ext TTY8664111010 prpl@cc.nih.gov<br>Sponsors and Collaborators<br>National Institute of Neurological Disorders and Stroke (NINDS) |
| Outcomes | Primary Outcome Measures :<br>Change in seizure frequency [ Time Frame: Baseline and 1 year ]<br>Change in seizure frequency, as measured by the Engel scale before and 1 year after treatment.<br><br>Secondary Outcome Measures :<br>1. Neurophysiological correlates of human cognitive function and to provide invasive monitoring for patients with tumor related epilepsy [ Time Frame: Baseline and 1 Year ]<br>The proportion of patients who are able to completely withdrawn from anti-epileptic medication (measured 2years after surgery; subjects will remain on antiepileptic medications for one year after surgery, and may be withdrawn from antiepileptic medications during the second year after surgery).<br><br>2. Neurophysiological correlates of human cognitive function and to provide invasive monitoring for patients with tumor related epilepsy [ Time Frame: Baseline and 1 Year ]<br>The proportion of patients who are seizure-free (Engel Class I) one year after surgery.<br><br>3. Neurophysiological correlates of human cognitive function and to provide invasive monitoring for patients with tumor related epilepsy [ Time Frame: Baseline and 1 Year ]<br>Mean Engel Class one year after surgery stratified by type of surgical procedure performed.<br><br>4. Neurophysiological correlates of human cognitive function and to provide invasive monitoring for patients with tumor related epilepsy [ Time Frame: Baseline and 1 Year ]<br>Permanent neurological deficits, assessed one year after surgery.<br><br>5. Neurophysiological correlates of human cognitive function and to provide invasive monitoring for patients with tumor related epilepsy [ Time Frame: Baseline and 1 Year ]<br>Neurophysiologic correlates of cognitive function and seizures<br><br>6. Neurophysiological correlates of human cognitive function and to provide invasive monitoring for patients with tumor related epilepsy [ Time Frame: Baseline and 1 year ]<br>Outcomes for subjects with tumor related epilepsy will be assessed under a separate protocol, 16-N-0041, Tumor Related Epilepsy |